

- C² control
29. [NEW] The genetically recombinant tobacco or alfalfa plant of Claim 16, which is stably transformed to contain and express a gene sequence which encodes *T. reesei* CBH I.
30. [NEW] The genetically recombinant tobacco or alfalfa plant of Claim 16, which is stably transformed to contain and express a gene sequence which encodes *A. cellulolyticus* endoglucanase E1.
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REMARKS

Claims 16-22 and 26 remain in the case. Favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in the order in which they appear.

Rejection of Claims 16-22 and 26 Under 35 U.S.C. §103(a) Over Van Ooyen et al. in View of Virki et al., Henrissat et al., and Willmitzer et al., and Further in View of Shiyaron et al. and Thomas et al.:

This rejection is respectfully traversed because the Office has improperly shifted the burden of presenting a *prima facie* case of obviousness. The Office bears the burden of presenting a *prima facie* case of obviousness, not the Applicants. Applicants respectfully submit that the Office has not presented a *prima facie* case of obviousness and is now improperly shifting the burden of going forward onto Applicants.

The Office states, at page 3 of the Office Action, that:

Applicants have not provided any clear evidence that it would require one of skill in the art undue experimentation to use the plant transformation system disclosed in Van Ooyen et al. to express the plant polysaccharide degrading enzymes according to SEQ. ID. NO: 8 and 9 in either a tobacco plant or an alfalfa plant.

Applicants respectfully submit that this requirement is improper. It is not Applicants' burden to show that the applied reference requires undue experimentation to

arrive at the claimed invention. The burden is upon the Office to show that the applied reference provides sufficient evidence to arrive at the present invention with a reasonable likelihood of success. Applicants respectfully submit 1) that this has not been done; and 2) that the Office is improperly using Applicants' own specification in support of this rejection.

In short, taken only in combination with the other prior art references, and without any prior knowledge of Applicants' own specification, the Van Ooyen reference, in combination with the other references, fails to provide any reasonable expectation of success because transformation of a plant host is not nearly as "precise and predictable" a method as Van Ooyen would have the Office believe. In short, whether or not a given plant host will express a functional heterologous enzyme is wholly unpredictable *a priori*. It is only after the expression is attempted can success be predicted with any reasonable degree of likelihood.

Applicants further traverse the rejection on the merits because even if the combination of references is made, the combined references fail to render obvious the claimed invention.

The Office cites in support of this rejection Van Ooyen's statement that "Changing plant characteristics through genetic engineering is a precise and predictable method...." At best, this statement is wildly optimistic. In fact, it is wholly unsupported in the reference itself. Furthermore, it is notoriously well known that plant transformation is subject to all kinds of pitfalls and unpredictable outcomes. It is anything but "precise and predictable." Gene silencing, for example, yields a transformed host that still fails to express the transgene. If more than one copy number of the transgene is transferred, co-suppression and instability can result. (Note that the claims positively require the host to be "stably" transformed.") Also, for sake of pointing out the gross over-generalization of the above statement, transformation of monocots surely is not "precise and predictable."

As objective evidence of the unpredictability of trying to transform a dicot plant host (i.e., a host analogous to the tobacco and alfalfa recited in the claims) with a known gene, using *Agrobacterium*-mediated transformation, see the attached reference from the

December 2001 edition of *Science in China*, entitled “Co-Suppression in transgenic *petunia hybrida* expressing chalcone synthase A (*chsA*),” (Yan et al.). Here, the authors describe an attempt to transform *chsA* into petunia (a dicot) using Agrobacterium-mediated transformation. Co-suppression occurred, resulting in a complete failure of the transformed plant to express the *chsA* gene. Note especially the discussion in the first paragraph stating that gene suppression is “unexpected,” that is, it cannot be predicted *a priori*. Note also the statement at the bottom of the first page of the reference: “The occurrence of co-suppression has caused failures of many cases of genetic engineering....” Most importantly, note the authors' conclusion of their own work at page 7 of the reference: “In this research the co-suppression rate was 100%.” In other words, using the conventional Agrobacterium approach in an effort to transform into a petunia host (an extensively utilized dicot plant host) a known gene for chalcone synthase A, the authors of this paper failed entirely to generate a single successful transformant. Their failure was not one of kind or degree, but one of complete and utter lack of success; the co-suppression rate was 100%. They did not generate a single successful dicot transformant. Using a known gene sequence, a well-known dicot plant host, and utilizing Agrobacterium-mediated transformation, these researchers failed entirely to transform the plant host. Note further that this paper was authored in December of 2001, and thus is very, very recent.

Thus, as evidenced by the attached Yan et al. paper, transforming a plant host with a known gene sequence is neither precise, nor predictable. This is so even when the gene target is known. Thus, the teaching of Shiyaron et al. and Thomas et al. does not address this fundamental problem. Yan et al. had the *chsA* gene at their disposal, used a well known host (petunia), and used the same Agrobacterium-mediated transformation method as described in both the present application and in Van Ooyen. Yet, the Yan et al. team was entirely unsuccessful.

Moreover, even in the absence of Yan et al. reference, if the shoe were on the other foot, the Office surely would not be as generous in its reading of the Van Ooyen reference. For example, had the Applicants exemplified a handful of transgenic plants that

successfully expressed two or three different types of heterologous enzymes, and then submitted a claim drawn to any plant host expressing any transgenic protein, the Office would undoubtedly reject such a claim as being overly broad and unsupported by the specification. Yet the Office quotes Van Ooyen's wholly unsupported statement in exactly the same fashion. That is the Office accepts, without any support at all, that Van Ooyen's statement "Changing plant characteristics through genetic engineering is a precise and predictable method" is the unassailable truth.

As evidenced by the Yan et al. paper, however, Van Ooyen's statement simply is not true. Plant transformations are unpredictable. The Office regularly assumes as much in its routine examination of biotech patent applications. Although not a black-letter requirement of the patent law, Applicants are encouraged to submit working examples of their biotech inventions for the sole reason that the Office regularly asserts the unpredictability of the biotech arts to support rejections under §112, first paragraph. In the reverse direction, Applicants submit that the Office is now taking an overly solicitous view of what can be predicted based upon the teaching of the Van Ooyen reference.

This issue boils down to two straightforward questions:

1) Can *Agrobacterium*-mediated transformation be used to transform any and all plant hosts to contain and express any and all heterologous gene sequences?

2) If the answer to the first question is "No," what types of heterologous proteins can be successfully and stably incorporated into what types of plant hosts using *Agrobacterium*-mediated transformation?

Applicants submit that the answer to the first question is unequivocally "no," as shown by the Yan et al. reference. Plant transformation using *Agrobacterium* as a vector is an unpredictable science and *Agrobacterium*-mediated transformation will not function to transform successfully any plant host with any heterologous gene sequence. Applicants submit that the answer to the second question is unknown and unpredictable until the transformation is actually attempted. Thus, the combined reference fail to render obvious the present invention because they do not provide a reasonable likelihood of success in arriving at the now-claimed invention.

At best, the combined references present a case of “obvious-to-try.” But, as noted in their earlier response “obvious-to-try” is not a proper basis on which to support a *prima facie* case of obviousness. On this point, Applicants note that the Office did not address their earlier argument regarding when an invention is “obvious-to-try” and thus patentable, versus when an invention is obvious, and thus unpatentable. Applicants again reiterate their position that the combined references, at most, present a case of “obvious-to-try,” but fall well short of the standard of *prima facie* obviousness required to sustain a rejection under §103.

The law of obviousness in this regard is straightforward: if one or more references provide technical motivation for arriving at the claimed invention, the combined references must provide a reasonable expectation of success. Such a reasonable expectation is lacking in the present rejection because the combined documents neither provide sufficient direction to arrive at the present invention, nor do they enable the present invention. As evidenced by the Yan et al. reference, plant transformation using *Agrobacterium* as a vector is unpredictable. Thus, the question of whether the enzymes recited in the present claims *could* be expressed using the approach described in Van Ooyen is entirely speculative. The answer to that question can only be determined after it is attempted—an experiment that is not described in the Van Ooyen reference. Thus, while one may be led to attempt to express the recited enzymes in a plant host after reading Van Ooyen, it is by no means a certain conclusion that the attempt will be successful, or even if the attempt might possibly be successful. The attempt might result in a complete and abject failure, in the same fashion as Yan et al's attempt to transform the petunia.

Thus, as noted earlier, the combined references present nothing more than possibilities for further research. Van Ooyen's huge list of enzymes does not provide “guidance” to arrive at the now-claimed invention, but merely suggests optimistic possibilities of enzymes that might be transformable into a plant host. It is equally likely, as evidenced by the Yan et al. paper, that an equal number of these listed enzymes cannot be successfully transformed into a plant host. Further still, the Van Ooyen reference

provides essentially zero guidance on which enzymes will work and which enzyme won't.

Again, the case of *In Re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), provides the guidelines for when an invention is "obvious-to-try" versus when an invention is obvious:

An invention is merely obvious-to-try if it is necessary:

to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (7 USPQ2d at 1681, citations omitted.)

Second, an invention is only obvious-to-try where the inventors:

explore[d] a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (*Ibid.*)

Van Ooyen et al. fail to say which of the huge number of enzymes listed in the document can actually be transformed successfully into a plant host using *Agrobacterium*-mediated transformation. Van Ooyen et al. fail to provide any information regarding the possibility of co-suppression. Van Ooyen et al. fail to address possible deleterious effects of transforming a cellulose-degrading enzyme into a plant host (plants being entirely reliant upon cellulose for their physical structure).

Moreover, the combined prior art references do not (and cannot) provide any indication of which parameters are critical, nor does the prior art provide any direction as to which of many possible choices is likely to be successful because none of the applied references, taken alone or in any combination, disclose the production of a transformed plant host that expresses the enzymes positively recited in the claims.

The combined references provide only the most general guidance as to how to achieve the presently claimed invention. Van Ooyen admittedly does not teach the claimed invention, nor do the secondary references. The huge number of variables, and lack of any unifying predictive theory of successful transformation and expression of recombinant enzymes in plants negates the assumption that the expression of alpha-

amylase and glucoamylase in a plant host, as described by Van Ooyen et al., renders obvious the transgenic production of the presently recited enzymes.

Combining Van Ooyen et al. with the secondary references to Virki et al., Henrissat et al., and/or Willmitzer et al. simply does not provide the concrete teaching or suggestion, with a reasonable likelihood of success, that is required by §103.

For sake of argument only, Applicants do not necessarily disagree with the Office's assertion that the references taken as a whole evidence a motivation to produce enzyme in plant hosts. But the mere motivation, without providing a reasonable likelihood of successfully arriving at the claimed invention, cannot give rise to a *prima facie* case of obviousness.

The Office expresses uncertainty at Applicants' discussion regarding the Virki et al. and Willmitzer et al. references. The disclosure of Virki et al. is limited to a description of the chromatographic fractionation of commercially-obtained cellulase mixtures and, according to the Office, "improving the nutritional value of crops" by treating them with cellulolytic enzymes. The present claims, however, are not directed to the enzymes themselves. Nor are the present claims drawn to treating plant material directly with the recited enzymes. Specifically, Claim 26 is directed to a method of ensilement comprising ensiling plant material with the transgenic plant of Claim 16. Insofar as Virki et al. do not even address transgenic plants, nor do they address co-ensilement of non-transformed plant material with the claimed transgenic tobacco or alfalfa of Claim 16, this reference is irrelevant to the present claims.

The same can be said of the Willmitzer reference. The Office candidly admits that:

Although the term "ensilement" is not specifically mentioned in these references, one of skill in the art would recognize that the teachings of Willmitzer et al. would necessarily encompass a method of ensilement. (See Office Action, page 6, bottom.)

Why? If the Willmitzer et al. reference is silent on the matter, why would someone of skill in the art assume that Willmitzer is discussing ensilement?

Moreover, ensilement with what? None of the references directly address ensilement with a transgenic plant. Virki et al. do not - they discuss treating plants with

cellulolytic enzymes obtained by conventional bacterial fermentation. Van Ooyen does not. Willmitzer et al. do not. Henrissat, like Virki et al. is concerned solely with treating plants with purified enzyme mixtures derived from microorganisms. Henrissat does not teach a method of ensiling that utilizes transformed plants. The Henrissat reference is totally silent regarding transformed plants that express any type of cellulose-degrading enzyme.

Applicants point here is that Claim 26 is not drawn to ensiling plants and adding a particular enzyme to the ensiled materials. Claim 26 positively requires that the transgenic plant recited in Claim 16 be included along with the ensiled materials. It is respectfully submitted that the combined references fail entirely to mention, motivate, suggest, or teach ensiling plant materials with a transgenic plant as recited in present Claim 16.

Applicants earlier point regarding the Henrissat and Virki references is that there is not motivation whatsoever to combine these two references in the first place: their conclusions are diametrically opposite. There simply is no technological motivation to combine these two references. Henrissat teaches that cellulase mixtures are desirable. Virki et al. teaches that cellulase mixtures are undesirable. See the first paragraph of the Summary of the Invention in Virki et al:

It has now been surprisingly found that the adverse effects of the commercial products are caused by the presence of certain enzyme combinations in the commercial grade cellulases used in said products.

Thus, there is an insurmountable barrier to combining these two references in the first place: Virki et al. teach that it is undesirable to combine cellulases, and therefore describes a means to fractionate the mixtures into their component enzymes. Henrissat teaches that the combinations are desirable. The two documents are irreconcilable. Thus, there is no technical motivation for them to be combined in this rejection.

For the above-noted reasons, Applicants respectfully submit that the rejection of Claims 16-22 and 26 under 35 U.S.C. §103(a) over Van Ooyen et al. in view of Virki et al., Henrissat et al., and Willmitzer et al., and further in view of Shiyaron et al. and Thomas et al. is improper. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 16-18 and 21-22 for Obviousness-Type Double-Patenting:

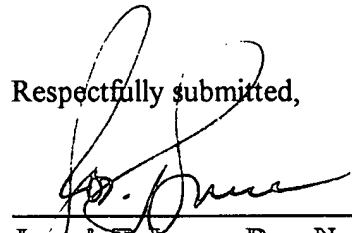
This rejection is believed to have been overcome by the Terminal Disclaimer (and fee) and Statement Under 37 CFR 3.73(b) filed herewith. Applicants respectfully request entry of the same.

In light of the Terminal Disclaimer, Applicants respectfully submit that this rejection has now been rendered moot. Withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,



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Signature: Marcia Layton